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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,998	06/14/2001	Maria Adele Pacciarini	01-270	1122

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EXAMINER	
OWENS JR, HOWARD V	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,998	PACCIARINI ET AL.	
	Examiner	Art Unit	
	Howard V Owens	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14 and 18-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,13,18-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Arguments

The following is in response to the amendment filed 3/12/04:

An action on the merits of claims 13, 14, 18-31 is contained herein below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 U.S.C. § 103

Applicant's arguments filed 3/12/04 have been fully considered but they are not persuasive. The rejection of claims 13, 14, 18, 19 and 20-31under 35 U.S.C. § 103 as being unpatentable over Kuhl et al., Cancer Chemotherap. Pharmacol., 33(1), pp. 10-16 (abstract) in combination with Miura et al., Gan To Kagaku Ryoho 25(9), 1262-5 (English abstract) and Gorbunova, Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver is maintained for the reasons of record.

Claims 13 and 14 are drawn to a pharmaceutical composition which comprises MMDX and a pharmaceutically acceptable agent, iodized oil, which remains selectively in a liver tumor after its injection through the hepatic artery.

Claim 18 is drawn to a method for treating a human liver tumor which comprises intrahepatic administration of a therapeutically effective amount of MMDX to a patient in need thereof. Dependent claims 20-31 are drawn to intrahepatic artery administration of MMDX.

Claim 19 is drawn to a method for reducing systemic exposure of a patient suffering from a liver cancer which comprises the intrahepatic administration of a therapeutically effective amount of MMDX to said patient.

Miura et al. teach the treatment of liver tumors or hapatocellular carcinomas of via hepatic artery administration of doxorubicin and lipiodol (iodized oil) to decrease tumor volume or cause remission. However it does not teach the use of MMDX, a doxorubicin analog, via hepatic artery administration.

Kuhl teaches that MMDX as a doxorubicin analog, not only has the same tumor specificity as doxorubicin, it is activated in the liver to a metabolite whose potency is 10 times greater and Gorbunova provides the nexus for intrahepatic arterial infusion as it teaches that IHAIC creates super high concentrations of an antitumor agent in the organ affected, which adequately bridges the nexus between the prior art and the invention as claimed.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to administer MMDX via the hepatic artery.

A person of ordinary skill in the art would have been motivated to use MMDX in hepatic artery administration since the prior art recognizes that hepatic artery administration of doxorubicin is beneficial for decreasing tumor volume within hepatic carcinomas and reducing systemic exposure via direct administration to the organ; moreover, one of skill in the art would have a reasonable expectation of success in the use of a more potent analog of doxorubicin, MMDX, in the same method of treatment.

Applicant's primary argument is that intrahepatic arterial administration of MMDX is not taught; however, as cited supra, for the combination of MMDX with iodized oil, Miura et al. teach the treatment of liver tumors or hapatocellular carcinomas of via hepatic artery administration of doxorubicin (of which MMDX is an analog) and lipiodol (iodized oil) to decrease tumor volume or cause remission. For lone use of MMDX, Gorbunova teaches that intrahepatic arterial administration of a chemotherapeutic creates super high concentrations in the organ affected, this localization of treatment is clearly beneficial for reducing systemic exposure. Applicant's assertion that MMDX as an analog could not be expected to behave like doxorubicin is also not persuasive. Applicant's assertions do not serve as fact and applicant has produced no evidence that the analog MMDX is so varied in it's structure, effect and target that one of skill in the art would not have a reasonable expectation of success. MMDX is not just a member of the class of anthracyclines, it is an analog of doxorubicin, and as cited supra, Kuhl teaches that "MMDX as a doxorubicin analog, not only has the same

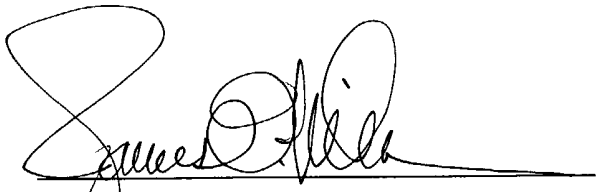
tumor specificity as doxorubicin, it is activated in the liver to a metabolite whose potency is 10 times greater". Given that doxorubicin and MMDX are analogs of one another with the same tumor specificity, in the absence of evidence to the contrary, applicant's assertions regarding the prior art and the expectation of one of skill in the art are not convincing.

Applicant attempts to demonstrate that one of skill in the art could not know how the MMDX analog could behave because they have effects on different Topoisomerase enzymes; however, if it is known what enzymes are affected by each compound, one of skill actually would know what the activity was for either doxorubicin or MMDX and not be unclear on the activity to such a degree that there could be no reasonable expectation of success. Applicant's arguments regarding the use of MMDX for only blood tumors and not solid tumors as cited supra, Kuhl teaches that MMDX has the same specificity as doxorubicin, as such applicant's comparison of epirubicin to doxorubicin does not refute the teachings of Kuhl nor is it probative for establishing whether there is a reasonable expectation of success in the use of MMDX with solid tumors given the teachings of Kuhl, noting that the standard is a reasonable expectation, not a guarantee.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Howard V. Owens
Patent Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Howard Owens whose telephone number is (571) 272-0658 . The examiner can normally be reached on Mon.-Fri. from 8:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Supervisory Patent Examiner signing this action, James O. Wilson can be reached on (571) 272 - 0661.